Articles

Tuberculosis Chemoprophylaxis

SHELLEY SALPETER, MD, *San Jose, California*

The incidence of tuberculosis in the United States, after decreasing for many years, has recently begun to climb at an alarming rate. This rise is due mainly to excess cases in high-risk groups including human immunodeficiency virus-infected patients, the elderly, the foreign born, and the homeless. In the United States tuberculosis has been associated with a 10% mortality despite adequate treatment.

The tuberculin skin test is a safe and inexpensive test for detecting tuberculous infection. To improve its predictive value the diagnostic criteria for classifying a positive reaction have recently been revised. High-risk populations should be screened to identify those persons who would most benefit from preventive treatment. Isoniazid therapy taken for 6 to 12 months is a safe and highly effective means of preventing tuberculous infection from developing into active disease. The most worrisome toxicity of isoniazid, fatal hepatitis, is extremely rare; when patients are monitored closely the incidence of death from hepatotoxicity is less than 0.01%.

(Salpeter S: Tuberculosis chemoprophylaxis. West J Med 1992 Oct; 157:421-424)

A successful preventive treatment strategy against a disease must meet certain requirements. There must be a clearly identifiable population at risk in whom screening efforts can be concentrated and preventive treatment targeted. There should be a good screening test with high predictive value that is safe and inexpensive. Finally, there must be an effective preventive treatment where the benefits far outweigh the risks. I will discuss an effective preventive treatment strategy against tuberculosis that if followed could substantially curtail the spread of the disease.*

Epidemiology of Tuberculosis in the United States

The incidence of active tuberculosis (TB) in the United States is about 10 cases per 100,000 per year.[1,2] More than 10 million people, or 5% of the population, have asymptomatic infections.[1] A person with a recent infection is at much higher risk for activation within the first year (5%) compared with someone with a remote infection (0.2% per year).[1,3] More than 90% of the total cases each year, however, are from the large pool of remote infections.[1]

Tuberculosis has been associated with a 10% mortality, occurring mainly in persons 65 years or older.[4,5] In more than half the cases the diagnosis is made after death.[6] Causes of death include pneumonia, hemorrhage, intestinal perforation, and meningitis.

The incidence of TB had been gradually declining in the United States for 40 years, but since 1985 it has been steadily climbing.[2] This rise is due in large part to the increasing number of cases in persons with the human immunodeficiency virus (HIV).[2,7] A prospective study done at a methadone-maintenance center showed that TB developed in HIV-infected persons with positive tuberculin skin tests at a rate of 8% per year.[8] The cumulative incidence of TB in HIV-infected patients is 2% per year, for a relative risk of 100 to 500 times average.[3,7,8]

Tuberculosis in HIV-infected patients tends to present atypically, with extrapulmonary or disseminated disease.[9] Active pulmonary disease is also atypical, often presenting with infiltrates in all lung fields or with mediastinal and hilar adenopathy. Tuberculosis in HIV-infected patients usually occurs early in the course of the disease, before or concurrent with the development of the acquired immunodeficiency syndrome (AIDS).[8,10] The Centers for Disease Control recently revised the case definition of AIDS to include extrapulmonary TB in HIV-infected patients.[11] All persons with TB or tuberculous infection should be tested for HIV because the management of seropositive patients is different from that for the general population.[9]

Many other groups are at high risk for TB developing.[12,13] The prevalence of asymptomatic infections approaches 50% in immigrants from Asian and Latin American countries, some elderly nursing home patients, the homeless, and underserved minorities.[3,14-17] Groups at high risk for activating latent infection include close contacts of patients with active pulmonary TB, those whose skin tests recently converted from negative to positive, persons with abnormal chest radiographs consistent with old TB, persons with alcoholism, and drug injecters.[12] Medical conditions that increase the risk of activation are immunosuppression (including corticosteroid use), silicosis, end-stage renal disease, diabetes mellitus, malnutrition or notable weight loss, and certain malignant neoplasms, including leukemia, lymphoma, and carcinomas of the upper gastrointestinal tract.[12] Clinical studies have not yet clarified the specific relative risks these conditions carry, but empiric evidence indicates that there may be at least a fourfold risk for activation.[4,13]

Tuberculosis Screening

The best test currently available to detect TB infection is the skin test using purified-protein derivative tuberculin. An intermediate-strength test containing 5 tuberculin units (TU) is administered intradermally to cause a delayed hypersensitivity reaction.[18] Strengths other than 5 TU should not be used because their biologic activities have not been quanti-

*See also "Treatment Strategies in the Prevention of Tuberculosis," by Thomas L. Petty, MD, on pages 463-465 of this issue.

From the Santa Clara Valley Medical Center, San Jose, California.
Reprint requests to Shelley Salpeter, MD, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
TB = tuberculosis

fied.[18] After the tuberculin is administered, the amount of induration is determined at 48 to 72 hours, but it usually remains positive for as long as a week.[15] If the reaction is negative, the test should be repeated. A positive reaction indicates a recall of immunity that may have waned over the years. This booster phenomenon is most common in persons aged 55 or older and can be seen from a week to a year after a previously negative test.[18-20] Persons who are screened on a yearly basis should receive this two-step testing to minimize confusion between a boosted reaction and a true conversion because treatment options differ for these two groups.[18,20] In addition, testing should be repeated in anyone who may have decreased immune responsiveness. This includes older persons and those with HIV infection or concomitant illness. Controls are often used to test for anergy, which is common in ill patients.[18]

To maximize the predictive value of the tuberculin skin test, the diagnostic criteria for a positive reaction have recently been revised.[18] A reaction of 5 mm or greater is considered positive for close contacts of infectious patients, persons with known or suspected HIV infection, and persons with a clinical suspicion of tuberculous infection or disease (characterized by an abnormal chest radiograph or symptoms). This low cutoff maximizes sensitivity while maintaining a fairly high specificity. A reaction of 10 mm or more is considered positive for persons from any other high-risk or high-prevalence group.[18] This broad category includes health care workers and even the general population of California (R. Saw, MD, State TB Control Program, written communication, July 1990).[18] In most of the United States where the prevalence of TB is low, the cutoff is increased to 15 mm for persons without any risk factor.[18]

It is important to remember that all patients with a positive tuberculin skin test must have active disease ruled out.[13] This is usually accomplished with a chest x-ray film, and if that is abnormal, then sputum specimens are obtained for acid-fast stains and culture. Extrapulmonary manifestations of TB have been increasing in frequency, especially in patients with HIV infection, and should be considered in the workup. If active disease is suspected, it is important to start antituberculous treatment while awaiting culture results.[13] It is often difficult to differentiate active from inactive disease on chest radiographs, and in those cases comparison with old films can be helpful. Stable chest films for at least four months provide good evidence for inactive disease.[18]

Chest radiographs consistent with old TB usually show fibrotic changes in the apices and pleura.[18] The amount of scarring seen appears to be proportional to the bacillary load and the risk for activation, which may be as high as 5% per year.[13,21] Those with substantial fibrosis on chest films require longer courses of isoniazid, which will be outlined later. Solitary calcified granulomas are thought to carry no increased risk for activation.[21]

Recommendations for Screening

There is no consensus on recommendations for who should be screened and how often. It is clear that screening efforts should be concentrated on high-risk groups and those people in contact with high-risk groups, such as health care professionals.[12,18] The test could be repeated on a yearly basis or even more often for some high-risk groups.[12,22] To reach many high-risk persons who have minimal contact with the health care system, skin testing programs should be set up at facilities such as shelters for the homeless, immigration offices, welfare departments, prisons, and long-term care facilities.[12,14,22] In addition, every adult in the United States should probably be screened at least once.[22]

Persons with previous bacille Calmette-Guérin vaccination have a gradual waning of tuberculin responsiveness over time. They should be screened and treated as if they were never vaccinated.[18] The vaccine, derived from a strain of *Mycobacterium bovis*, has been available for many years, but studies have shown that it offers minimal to no protection against the development of TB, and its use has been largely abandoned in adults.[13]

Isoniazid Chemoprophylaxis

Chemoprophylaxis with 300 mg of isoniazid—10 mg per kg for children—given daily for 6 to 12 months has been used to decrease the risk of active TB developing.[13] The efficacy of chemoprophylaxis ranges from 65% to 98%, depending on the length of treatment and level of compliance.[4,21,23-25] Protection lasts for at least 20 years and presumably for life.[13] In healthy patients with normal or minimal chest film findings, a 6-month course of treatment is as effective as a 12-month course and is more cost-effective.[21,23,25] The efficacy of prophylaxis in HIV-infected patients has not yet been documented, but the good response to standard chemotherapy for active disease suggests that a 12-month course of isoniazid should be effective as preventive therapy.[9,10]

Risks of Isoniazid Therapy

Transient asymptomatic elevations of aminotransferase levels occur in 10% to 20% of patients and carry no increased risk for hepatitis.[13] The risk for clinical hepatitis in young healthy adults is 0.3%, but this can increase to as much as 2.6% for those with daily alcohol use, chronic liver disease, and advanced age.[26]

Fatal hepatotoxicity is much rarer than previously estimated. A survey from 1972 showed 8 deaths in almost 14,000 patients treated with isoniazid.[26] All of the deaths were in patients older than 35, and most were in patients with severe alcoholism who were not receiving routine monitoring for liver function abnormalities.[26,27] There have subsequently been several prospective clinical trials and epidemiologic surveys that observed more than 14,000 patients on isoniazid therapy with improved monitoring guidelines, and no fatal hepatotoxicity has been found.[24,28-38] Peripheral neuropathy occurs rarely with isoniazid therapy and is preventable with 10 to 25 mg of pyridoxine hydrochloride a day.[39] Vitamin B_6 should be added only for patients at higher risk for neuropathy developing.[13] Risk factors include age older than 65, pregnancy, diabetes mellitus, chronic renal failure, alcoholism, treatment with anticonvulsants, and malnutrition.

Another side effect from isoniazid therapy is a vague impairment of concentration, which may be avoided by administering the dose at night.[39] Gastrointestinal symptoms, dizziness, acne, and allergic rashes have also been reported.[28,29]

Special Precautions With Isoniazid Use

There are a few absolute contraindications for isoniazid treatment.[13] The medicine should not be given to someone who has previously had a severe isoniazid hepatitis or a hypersensitivity reaction (like fever, rash, or arthritis). Isoniazid treatment should also be avoided in patients with acute liver disease.

Pregnancy is not an absolute contraindication for isoniazid therapy. No teratogenicity has been documented with its use, and it has been used in pregnant women with active TB, even in the first trimester.[13] A recent study, however, reported fatal isoniazid hepatitis in two young women shortly after delivery.[40] No prospective trials or surveys have been published to assess the risk in pregnant and postpartum women, but it is reasonable to withhold preventive therapy until after delivery, unless there is a high risk of TB activation. In those patients, treatment could begin after the first trimester with close patient monitoring.[13]

The concurrent use of phenytoin with isoniazid may be associated with increased serum concentrations of both drugs. Phenytoin levels should be monitored and the dose adjusted as needed.[13] Similarly, isoniazid interferes with the metabolism of disulfiram, carbamazepine, anticoagulants, benzodiazepines, and vitamin D, often requiring a reduction in the dose of these drugs.[39] The dose of isoniazid in these cases should remain the same.

Patient Management on Isoniazid Therapy

It is recommended that all patients be monitored on a monthly basis for symptom review and to evaluate compliance.[13] This can be done in person or by telephone. If there are any symptoms that could indicate hepatic toxicity, therapy should be withheld pending the results of liver function tests. No more than 30 pills should be dispensed at one time. In addition to close monitoring of symptoms, patients at increased risk for hepatic toxicity, including all those older than 35, should get baseline and periodic liver function tests, possibly every two to three months. Isoniazid should be stopped if the aspartate aminotransferase level exceeds three to five times the upper limit of normal.[13]

Recommendations for Isoniazid Chemoprophylaxis

The current recommendations for who should receive isoniazid chemoprophylaxis are listed in Table 1.[13,41] The list includes all persons with a reaction of at least 5 mm who have known or suspected HIV infection, are close contacts of patients with infectious TB, or have fibrotic changes on chest radiographs after active TB has been ruled out. Persons in these categories who have negative skin tests associated with anergy should also receive chemoprophylaxis in certain situations. Anergic patients with HIV infection should be treated if they are close contacts of infectious cases or if there is a past history of a positive skin test.[13,42] In addition, chemoprophylaxis should be considered for anergic HIV-infected persons who come from a group in which the prevalence of TB infection is at least 10%.[42] This includes drug injecters, prisoners, residents of long-term care facilities, immigrants, the homeless, and underserved minorities. Close contacts younger than 18 years should be treated until the skin test is repeated at three months.[13] Note that it is recommended that patients with HIV infection or notable abnormalities on chest radiographs be treated for 12 months with isoniazid and all other patients should receive it for 6 months.[13,21,41]

The management of low-risk tuberculin reactors is controversial. The recommendation to withhold chemoprophylaxis for low-risk reactors older than 35 came as a result of the 1972 survey and has not been revised since, even though the risk of death in monitored patients appears to be negligible.[43] Some studies using decision analysis indicate that, even if there were a significant mortality, all persons with a positive reaction of an unknown duration would benefit from chemoprophylaxis regardless of age.[5,23] The benefit is even greater when considering the spread to others. It is estimated that each case of infectious TB ultimately gives rise to another case.[27] In certain situations, such as nursing homes, shelters for the homeless, or communal houses for AIDS patients, the risk for spread is substantially higher, and epidemics have been reported.[7,14,16,44] Preventive treatment should be considered for those reactors who pose the greatest threat for transmission, such as residents of long-term care facilities and health care professionals in contact with susceptible persons.[3,27,41] It is important to involve the patient in the decision-making process whenever possible. The risks and benefits of the treatment options could be outlined and the patient's preference elicited.

TABLE 1.—*Recommendations for Isoniazid Chemoprophylaxis*

Purified-Protein Derivative Induration	*Duration of Therapy, mo*
≥5 mm	
All persons with known or suspected HIV	12
All close contacts of those with infectious TB	6
All persons with abnormal chest radiographs (inactive)	12
≥10 mm	
All persons with recent tuberculin skin test conversion	6
All drug injecters (without HIV)	6
All persons with conditions that increase risk	6
≥10–15 mm	
Persons younger than 35	6

HIV = human immunodeficiency virus, TB = tuberculosis

Possible Alternatives to Chemoprophylaxis

Although no other drugs have clearly documented efficacy for prophylaxis, there are many situations in which alternative forms of treatment should be considered.[22] Rifampin, alone or in combination with other drugs, can be used for contacts of patients with known isoniazid-resistant TB, immigrants at high risk for isoniazid-resistant disease developing, or persons intolerant to isoniazid.[13,41,45] Preliminary data from experimental studies and ongoing clinical trials indicate that combinations of drugs given daily for two to three months have efficacies equal to a six-month course of isoniazid without increased toxicity.[36,46-48] Data from studies of patients with smear- and culture-negative pulmonary tuberculosis indicate that for reactors with substantial chest film findings, a four- to six-month course of two drugs may be equivalent to 12 months of isoniazid therapy.[32,33]

Soon we will probably be using short-course regimens as standard prophylaxis. The combinations of drugs may help combat the recent emergence of multiple-drug resistance.[49] Better compliance will be another advantage of this approach. If the toxicity turns out to be low, preventive treatment could be extended to include stable reactors of all ages and possibly eradicate the disease.

Discussion

Why, if we have an effective preventive treatment strategy, are we failing to control tuberculosis? To help answer that question, a retrospective study of 275 patients with active TB was done to evaluate if the disease could have been prevented.[50] A third of the patients had been out of the health care system for at least five years before TB developed, and they had not received screening. Another third had been seen by a health professional but were never screened. Of the third who had been screened, more than half had a positive skin test, but two thirds of the reactors (13% of the total cases) were not offered therapy. Less than 25% of the cases resulted from a failure in our present preventive treatment system, such as a lack of tuberculin sensitivity or isoniazid efficacy. The results of this study clearly indicate that better attention to the guidelines for screening and prophylaxis could have a substantial effect on the control of tuberculosis.

REFERENCES

1. Farer LS: The current status of tuberculosis control efforts. Am Rev Respir Dis 1986; 134:402-407
2. Rieder HL, Cauthen GM, Kelly GD, Bloch AB, Snider DE Jr: Tuberculosis in the United States. JAMA 1989; 262:385-389
3. Hamrick RM, Yeager H Jr: Tuberculosis update. Ann Fam Pract 1988; 38:205-213
4. Glassroth J, Robins AG, Snider DE Jr: Tuberculosis in the 1980s. N Engl J Med 1980; 302:1441-1450
5. Rose DN, Schecter CB, Silver AL: The age threshold for isoniazid—A decision analysis for low-risk tuberculin reactors. JAMA 1986; 256:2709-2713
6. Katz I, Rosenthal T, Michaeli D: Undiagnosed tuberculosis in hospitalized patients. Chest 1987; 6:770-774
7. Barnes PF, Bloch AB, Davidson PT, Snider DE Jr: Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 1991; 324:1644-1650
8. Selwyn PA, Hartel D, Lewis VA, et al: A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989; 320:545-550
9. Centers for Disease Control (CDC): Tuberculosis and human immunodeficiency virus infection: Recommendations of the Advisory Committee for the Elimination of Tuberculosis (ACET). MMWR 1989; 38:236-250
10. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC: Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med 1991; 324:289-294
11. CDC: Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; 36(No. 1-S):3S-9S
12. CDC: Screening for tuberculosis and tuberculous infection in high-risk populations. MMWR 1990; 39(No. RR-8):1-7
13. American Thoracic Society: Treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Respir Dis 1986; 134:355-363
14. Schieffelbein CW, Snider DE Jr: Tuberculosis control among the homeless populations. Arch Intern Med 1988; 148:1843-1846
15. Slutkin G, Perez-Stable EJ, Hopewell PC: Time course and boosting of tuberculin reactions in nursing home residents. Am Rev Respir Dis 1986; 134:1048-1051
16. Stead WW, Lofgren JP, Warren E, Thomas C: Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. N Engl J Med 1985; 312:1483-1487
17. Perez-Stable EJ, Slutkin G, Paz EA, Hopewell PC: Tuberculin reactivity in United States and foreign-born Latinos: Results of a community-based screening program. Am J Public Health 1986; 76:643-646
18. American Thoracic Society: Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 1990; 142:725-735
19. Stead WW, To T: The significance of the tuberculin skin test in elderly persons. Ann Intern Med 1987; 107:837-842
20. Thompson NJ, Glassroth JL, Snider DE Jr, Farer LS: The booster phenomenon in serial tuberculin testing. Am Rev Respir Dis 1979; 119:587-597
21. International Union Against Tuberculosis: Efficacy of various durations of isoniazid preventive therapy for tuberculosis: Five years of follow-up in the IUAT trial. Bull WHO 1982; 60:555-564
22. CDC: A strategic plan for the elimination of tuberculosis in the United States. MMWR 1989; 38(No. S-3):1-25
23. Rose DN, Schecter CB, Fahs MC, Silver AL: Tuberculosis prevention: Cost-effectiveness analysis of isoniazid chemoprophylaxis. Am J Prev Med 1988; 4:102-109
24. Stead WW, To T, Harrison RW, Abraham JH III: Benefit-risk considerations in preventive treatment for tuberculosis in elderly persons. Ann Intern Med 1987; 107:843-845
25. Snider DE Jr, Caras GJ, Koplan JP: Preventive therapy with isoniazid: Cost-effectiveness of different durations of therapy. JAMA 1986; 255:1579-1583
26. Koponoff DE, Snider DE Jr, Caras GJ: Isoniazid-related hepatitis: A US Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978; 117:991-1101
27. Comstock JW: Prevention of tuberculosis among tuberculin reactors: Maximizing benefits, minimizing risks. JAMA 1986; 256:2729-2730
28. Byrd RB, Horn BR, Solomon DA, Griggs GA: Toxic effects of isoniazid in tuberculosis chemoprophylaxis: Role of biochemical monitoring in 1,000 patients. JAMA 1979; 241:1239-1241
29. Bailey WC, Taylor SL, Dascomb HE, et al: Disturbed hepatic function during isoniazid chemoprophylaxis: Monitoring the hepatic function of 427 hospital employees receiving isoniazid chemoprophylaxis for tuberculosis. Am Rev Respir Dis 1973; 107:523-529
30. Grzybowski S, Ashley MJ, Pinkus G: Chemoprophylaxis in inactive tuberculosis: Long-term evaluation of a Canadian trial. Can Med Assoc J 1976; 114:607-611
31. Mehta JB, Dutt AK, Harvill L, Henry W: Isoniazid preventive therapy for tuberculosis: Are we losing our enthusiasm? Chest 1988; 94:138-141
32. Dutt AK, Moers D, Stead WW: Smear- and culture-negative pulmonary tuberculosis: Four-month short-course chemotherapy. Am Rev Respir Dis 1989; 139:867-870
33. Dutt AK, Moers D, Stead WW: Smear- and culture-negative pulmonary tuberculosis: Six-month chemotherapy with isoniazid and rifampin. Am Rev Respir Dis 1990; 141:1232-1235
34. Nazar V, Oberle M, Nolan C: Results of a directly observed intermittent isoniazid preventive therapy program in a shelter for homeless men (Abstr). Am Rev Respir Dis 1991; 141S:A438
35. Fitzgerald JM, Allen EA, Elwood RK, Chao CW: Isoniazid chemoprophylaxis in British Columbia 1982-1987 (Abstr). Am Rev Respir Dis 1990; 141S:A438
36. Geiter LJ, O'Brian RJ, Kopanoff DE: Short-course preventive therapy for tuberculosis (Abstr). Am Rev Respir Dis 1990; 141S:A437
37. Rabindran E, Matuszak DL, Israel E, et al: Preventive therapy for tuberculosis in Maryland. Maryland Med J 1991; 40:793-797
38. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council: A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992; 145:36-41
39. Pérez-Stable EJ, Hopewell PC: Current tuberculosis treatment regimens: Choosing the right one for your patient. Clin Chest Med 1989; 10:323-339
40. Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S: Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989; 104:151-155
41. CDC: The use of preventive therapy for tuberculosis infection in the United States: Recommendations of the Advisory Committee for the Elimination of Tuberculosis (ACET). MMWR 1990; 39(No. RR-8):9-12
42. CDC: Purified protein derivative (PPD)-tuberculin anergy and HIV infection: Guidelines for anergy testing and management of anergic persons at risk of tuberculosis. MMWR 1991; 40(No. RR-5):27-33
43. American Thoracic Society: Preventive therapy of tuberculous infection. Am Rev Respir Dis 1974; 110:371-374
44. CDC: Tuberculosis outbreak among persons in a residential facility for HIV-infected persons—San Francisco. MMWR 1991; 40:649-652
45. Schoetz DJ Jr, Graeme-Cook F: A 17-year-old Cambodian girl with recurrent abdominal pain and a tender mass in the right lower quadrant—Case records of the Massachusetts General Hospital: Case 44-1991. N Engl J Med 1991; 325:1295-1307
46. Grosset J: Present and new drug regimens in chemotherapy and chemoprophylaxis of tuberculosis. Bull Int Union Tuberc 1990; 65:86-91
47. Lecoeur HF, Truffot-Pernot C, Grosset JH: Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am Rev Respir Dis 1989; 140:1189-1193
48. Kapetaneas S, Rapti A, Arapis I, Chrisiotis C, Anagnostopulu U: Short-term chemoprophylaxis—Experience in Greece (Abstr). Am Rev Respir Dis 1990; 141S:A437
49. CDC: Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons—Florida and New York, 1988-1991. MMWR 1991; 40:585-591
50. Glassroth J, Bailey WC, Hopewell PC, Schecter G, Harden JW: Why tuberculosis is not prevented. Am Rev Respir Dis 1990; 141(pt 1):1236-1240